

consent requirement for a trial is more drastic than merely not spelling out a grim prognosis. The presumption of informed consent should surely be stronger.

The exceptions need fuller debate. Exceptions for those unconscious, or unable to understand the request, seem plausible. But can it be right to bypass the requirement of consent in the case of someone capable of understanding the request? With trivial risks it is hard to think many will be disturbed to be asked or will refuse. What about more major procedures? To waive the requirement of consent whenever the facts may cause distress seems virtually to abandon it. If a

particular patient with cancer of the prostate would be devastated by being told the facts, he could be excluded from the trial. It seems unlikely that everyone will be excluded on these grounds. If too few of the remainder would consent when asked, can it be right to impose such a trial on uninformed and unconsenting patients?

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1 Anonymous. Research ethics. *IME Bulletin* 1986;March:1-7.

2 Anonymous. News and notes. *IME Bulletin* 1986;April:11.

Penicillin: 1929-40

There has been much speculation and debate about the 11 "silent" years between 1929, when Fleming's first published article announced his discovery of penicillin,¹ and 1940-1, when the Oxford workers firmly established it as a major chemotherapeutic agent.^{2,3} Why did Fleming not push on with the kind of standard studies on animals then commonly used to assess antimicrobial agents? It was wrongly suggested—by Chain, for example⁴—that Fleming simply did not think of it. Apart from published evidence to the contrary,^{5,6} I clearly recall a visit which Fleming paid in 1932 to Professor John Cruickshank's bacteriology department in Aberdeen University. At that time I was the most junior member of that department, working on a scholarship. I was interested in a coccus which Professor Cruickshank had isolated and which inhibited growth of other bacteria. I showed it to Fleming, knowing of his publication on penicillin. Fleming showed polite interest but said it was not really anything very unusual; it had probably something to do with hydrogen peroxide production and was in any case not likely to be a good starting point for a beginner. "You'd need to work with a first rate biochemist," he said, and went on to explain why he had not pursued penicillin. Apparently Raistrick, the foremost expert in the chemistry of moulds, had failed to extract and purify penicillin without losing its antibacterial activity; so Fleming had decided that the great potentialities of penicillin—of which he was quite certainly fully aware—would have to await the future and a new biochemical approach. This new approach, made possible by the brilliant insights of Chain along with Heatley and Abraham, led in 1940 and 1941 to the two famous Oxford papers which introduced the antibiotic era.^{2,3}

There were hints from Fleming himself of the usefulness of penicillin—even impure and weak penicillin—in the treatment of local infections. These experiments are well described in Hare's excellent book on *The Birth of Penicillin*⁷ and in his publication in *Medical History*.⁸ One of the most encouraging experiments described was the successful treatment in 1932 of pneumococcal conjunctivitis in Fleming's colleague Dr K B Rogers. Apart from Raistrick's lack of success in concentrating purified penicillin Fleming was influenced by the very rapid excretion of penicillin from the blood of injected animals along with the observation that it killed bacteria only slowly. This theoretical consideration happily did not deter Florey when he made the crucial experiment in 1940 which Fleming (and others also)

could certainly have made at any time from 1930 onwards.

Wainwright and Swan have now published from Sheffield an extremely interesting paper which adds further evidence about early experiments with penicillin during the years between 1929 and 1940.⁹ Interestingly it was Florey who recalled that, at Sheffield, Dr Cecil George Paine, a young pathologist, had told him that he had successfully treated cases of conjunctivitis but had not published the results. Paine was a graduate of Fleming's hospital—St Mary's in London—and it was from Fleming that Paine secured a culture of the penicillin producing mould, but it was at the Royal Infirmary in Sheffield that he did his work on penicillin in 1930-1. The case notes of the late Mr A B Nutt, an assistant ophthalmic surgeon at Sheffield Royal Infirmary, and Paine's own records and recollections show that three patients with gonococcal neonatal ophthalmia, one with a staphylococcal eye infection, and one with a pneumococcal eye infection were treated successfully. The details now uncovered also clearly prove that Paine's work in Sheffield was done in late 1930 and early 1931—that is, before Florey's appointment as professor of pathology in 1932. The statement on page 219 of Macfarlane's book—to the effect that Paine's trials with penicillin were being made in 1932 in Florey's department at Sheffield⁶—is, therefore, erroneous; and so is another statement by Baldry to the same effect (page 106).¹⁰

It was Florey himself who reminded Masters, author in 1946 of *The Miracle Drug*, of Paine's work,¹¹ Florey knew of Paine's work because Paine told him about it.¹² Clearly it was others who linked Florey's Oxford work on penicillin with Paine's earlier work in Sheffield, which was done shortly before Florey took up his post in Sheffield. The misunderstanding was not surprising, but the detailed research now presented by Swan and Wainwright establishes that the account needs to be corrected in fairness to Paine.⁹

For his own part, Paine showed a creditably philosophical resignation to the real weight of his unpublished contribution—and how it might so easily have been so much greater and more accurately recorded in the histories of penicillin discovery. When Paine was asked by Wainwright at an interview where he placed himself in the penicillin story, he replied: "Nowhere—a poor fool who didn't see the obvious when it 'was stuck in front of him.'" In his modest remark Paine does himself less than justice. Paine's success with the ophthalmia infections was, indeed, the first clear and direct proof that penicillin had a useful place in clinical medicine,

and it may well be that Florey's knowledge of Paine's work, which Paine conveyed to him, led him to make the crucial experiment which others had not undertaken.⁸

Both Fleming and Paine were deterred by the unstable nature of the crude extracts of weak penicillin available to them. Yet even such weak impure penicillin would have proved effective in treating experimentally infected mice. Florey had two additional advantages. Chain had provided sufficient amounts of a stronger and less impure penicillin than Fleming and Paine had, and this raised the probability that a systemic antibacterial action could be secured by injection. Florey was also fortunate in that his own philosophical attitude to experiments was simple and direct. If you made the experiment it might fail or it might succeed. If you did not make the experiment it would certainly not succeed.

Fleming, on the other hand, may have been deterred by the expressed philosophy of Almroth Wright, his chief, who discouraged doing experiments in his department if reason made their success improbable or doubtful. This apparently ruled out penicillin: it was excreted rapidly from animals but it killed bacteria only slowly. Happily it soon arrested bacterial multiplication and did no harm to leucocytes, the first line of the body's natural defences against infection. There were also the long continued and discouragingly negative results of Ehrlich and his pupils, despite all the resources of the German chemical industry, in their attempts to produce a supply of "magic bullets" that would kill bacteria in the animal body. Salvarsan's action on spirochaetes remained the only good evidence of an agent effective against bacteria. The prevailing atmosphere was strongly sceptical up to 1934. The discovery of prontosil was still four

to five years away when Fleming and Paine were at work on penicillin; and the coming of later and even more effective sulphonamides in the later 1930s had revived hope that antibacterials might have a brighter future than had seemed likely in the period 1928-34.

Interestingly enough both Florey and Chain discouraged the idea that their work was motivated by a desire either to relieve suffering humanity or make a dramatic industrial scoop. Florey was simply interested in the mode of action of antibacterials, and Chain in the challenge represented by the apparent difficulty of purifying penicillin.

Politicians and Treasury mandarins should be reminded of the vast and unforeseen benefits that may accrue from allowing intelligent scientists to play themselves by exercising their skills on what they find interesting.

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Coeliac axis compression syndrome

The syndrome of abdominal pain associated with compression of the coeliac artery by the median arcuate ligament of the diaphragm was described in 1963.¹ It is sometimes known as the median arcuate ligament syndrome.² Most cynical vascular surgeons doubt the existence of this entity—yet, paradoxically, we are still prepared to operate when the omens are favourable. The operation consists of division of the median arcuate ligament; this results (possibly very importantly) in gross destruction of the coeliac autonomic ganglion. Reconstruction of the coeliac axis is sometimes advocated as part of the procedure. Anecdotal evidence suggests that patients have been cured of their pain,^{3,4} blood flow has increased in the artery concerned,⁵ and the results of the provocative xylose absorption test have improved in some patients after surgery.⁶

Nevertheless, anatomical compression of the coeliac axis by the median arcuate ligament is quite a common abnormality—with an incidence far exceeding that of the syndrome.^{7,8} Most of the published reports of good symptomatic results of the operation have been based on only brief follow up.⁷ One good long term study showed a considerable relapse rate with time, though angiograms were not repeated to exclude recurrence of compression.⁹ The patients, who are more frequently women than men, commonly have multiple symptoms. Most importantly, no patient with the syndrome

has ever been reported to have progressed to infarction of the viscera supplied by the coeliac axis. This, I believe, is very strong indirect evidence against the pain being ischaemic; conventional mesenteric angina progresses relentlessly to infarction. The relief of pain after the operation may be due only to the coincidental destruction of the coeliac ganglion.^{3,10}

The syndrome is diagnosed in patients in whom another cause of upper abdominal pain has been excluded, and the only specific physical sign is an epigastric bruit, which may become more high pitched or disappear in expiration when the position of the diaphragm changes¹¹; epigastric bruits are, however, common.¹² The presence of the anatomical abnormality is usually confirmed by lateral angiography, and with the advent of digital subtraction intravenous angiography the vessels may be visualised easily and safely.

A recent paper from Australia describing a very small series makes the point—probably true of most operations for abdominal pain—that patients tend to do better if they do not have a multitude of symptoms which might be functional.⁵ The authors proposed that the extent of the associated symptoms should be recorded in case reports. I would fully support that view; having operated on four such patients, I would not now operate on one with multiple symptoms but would be prepared to decompress the artery in a patient with severe pain, particularly when associated with loss of weight,